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| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/591,263 | RUSSELL ET AL. | |
| | Examiner | Art Unit | |
| | AMANDA SHAW | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

5)☒ Claim(s) *1,2,4,10-14,16,18-20,22,23,32-34,36,44-47,60,61,68,88 and 90-93* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-47, 60-61, 68, 88, and 90-93* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/3/2011, 6/20/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 8, 2011 has been entered.

2. Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-47, 60-61, 68, 88, and 90-93 are currently pending.

Claims 36, 60-61, 68 have been amended.

Claims 90-93 are newly presented.

After further consideration claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34 previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability.

Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-47, 60-61, 68, 88, and 90-93 are under examination.

Additionally it is noted that Applicants have elected the following species for examination:

A. the Protein C sequence (SEQ ID NO: 1)

B. the SNP at position 4732 of the Protein C sequence (SEQ ID NO: 1)

C. systemic inflammatory response syndrome (SIRS) as the disease

D. activated protein C as the anti-inflammatory agent

***Withdrawn Objections***

3. The objection made to the specification in section 5 of the Office Action of October 13, 2011 is withdrawn in view of the ADS filed on April 8, 2011.

***Claim Rejections - 35 USC § 101***

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 4, 10, 14, 16, 18- 20, 22, 23, 32, and 90-91 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Based upon consideration of all of the relevant factors with respect to the claim as a whole, the claims are held to claim an abstract idea, and is/are therefore rejected as ineligible subject matter under 35 U.S.C. 101. The rationale for this finding is explained below:

Claims 1, 2, 4, 10, 14, 16, 18-20, and 22-23 are drawn to a method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition, and are broadly drawn such they include an entirely mental analysis. The method requires single active process step of determining a genotype of said subject which includes one

or more polymorphic sites in the subject's protein C sequence. The determining step encompasses an entirely mental process whereby determining occurs via consultation with a medical file or a database of previously obtained genotype information. Thus, there is no recitation of a machine or transformation with is explicit or inherent in the practice of the claimed method. Here the general concept of the claim is disembodied, and the mechanism by which the steps are implemented is imperceptible. In the present situation, the claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing. Nor do the claims directly apply a law of nature in a practical manner with meaningful execution steps or implement more than a concept by performing observable and verifiable steps. These factors weigh heavily against the patentability of the subject matter, and thus it is found that the claims are drawn to an abstract idea. The unpatentability of abstract ideas was confirmed by the U.S. Supreme court in Bilski v. Kappos, No. 08-964, 2010 WL 2555192 (June 28, 2010). This rejection could be overcome by amending the claims to recite a step of "obtaining a nucleic acid sample and determining in the sample a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence".

Claim 32 is drawn to a method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition, an is broadly drawn such that it includes an entirely mental analysis. The method requires determining a genotype at one or more polymorphic

sites in the protein C sequence and sorting subject based on their genotype. The determining step encompasses an entirely mental process whereby determining occurs via consultation with a medical file or a database of previously obtained genotype information. Thus, there is no recitation of a machine or transformation with is explicit or inherent in the practice of the claimed method. Here the general concept of the claim is disembodied, and the mechanism by which the steps are implemented is imperceptible. In the present situation, the claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing. Nor do the claims directly apply a law of nature in a practical manner with meaningful execution steps or implement more than a concept by performing observable and verifiable steps. These factors weigh heavily against the patentability of the subject matter, and thus it is found that the claims are drawn to an abstract idea. The unpatentability of abstract ideas was confirmed by the U.S. Supreme court in Bilski v. Kappos, No. 08-964, 2010 WL 2555192 (June 28, 2010). This rejection could be overcome by amending the claims to recite a step of "obtaining a nucleic acid sample and determining in the sample a genotype at one or more polymorphic sites in the protein C sequence".

Claims 90-91 are drawn to a method of identifying a human subject at risk of death in whom treatment with activated protein C decreases said risk, and is broadly drawn such that it includes an entirely mental analysis. The method comprise: (a) selecting human subjects having an APACHE II score of >25 as an indication of the subjects' risk of death; and (b) selecting from the subjects selected in (a), those

subjects who also have (i) a CC or CT at 4732 of SEQ ID NO: 1; (ii) a genotype in SEQ ID NO: 1 that is in linkage disequilibrium with position 4732 in SEQ ID NO: 1, or (iii) a combination of genotypes in SEQ ID NO: 1 that are in linkage disequilibrium with position 4732 in SEQ ID NO: 1. The selecting steps encompass an entirely mental process whereby selecting occurs via consultation with a medical file or a database of previously obtained information. Thus, there is no recitation of a machine or transformation with is explicit or inherent in the practice of the claimed method. Here the general concept of the claim is disembodied, and the mechanism by which the steps are implemented is imperceptible. In the present situation, the claims are not directed to patent-eligible subject matter since they are not tied to any particular machine or apparatus and they do not require any particular article to be transformed into another state or thing. Nor do the claims directly apply a law of nature in a practical manner with meaningful execution steps or implement more than a concept by performing observable and verifiable steps. These factors weigh heavily against the patentability of the subject matter, and thus it is found that the claims are drawn to an abstract idea. The unpatentability of abstract ideas was confirmed by the U.S. Supreme court in Bilski v. Kappos, No. 08-964, 2010 WL 2555192 (June 28, 2010). This rejection could be overcome by amending the claims to recite a step of "obtaining a nucleic acid sample and determining in the sample a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence".

***Claim Rejections - 35 USC § 112 1st paragraph***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 10-14, 22-23, and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 10-14, and 22-23 are drawn to a method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition. The method comprises determining a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence. The wherein clause states that the genotype is indicative of an ability of the subject to recover from the inflammatory condition. The claims broadly encompass determining the genotype of the subject (human or non-human) with respect to one or more of an enormous and wide variety of allelic variants in the protein C gene. Thus the claims encompass determining many different protein C nucleic acid sequences wherein the protein C nucleic acid sequences are correlated with the ability of the subject to recover from the inflammatory condition. Nucleic acids of such a large genus have not been taught by the specification.

Claims 32-34 are drawn to a method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition. The method comprises determining a genotype at one or more polymorphic sites in the protein C sequence and sorting subjects based on their genotype. The wherein clause states that the genotype is indicative of an ability of the subject to recover from the inflammatory condition. The claims broadly encompass determining the genotype of the subject (human or non-human) with respect to one or more of an enormous and wide variety of allelic variants in the protein C gene. Thus the claims encompass determining many different protein C nucleic acid sequences wherein the protein C nucleic acid sequences are correlated with the ability of the subject to recover from the inflammatory condition. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of the protein C gene (SEQ ID No. 1) and discloses several polymorphic variations of SEQ ID NO: 1. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 is correlated with decreased survival and increased multiple organ dysfunction. The specification further describes additional polymorphic variations that are in linkage disequilibrium with position 4732. Of the polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at

position 4800 ($r^2$ value of 0.85), was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification does not provide any characteristics that would allow one to identify any particular polymorphic variants of the disclosed sequence that are correlated with a decreased likelihood of recovery from an inflammatory condition or an increased risk of having a poor outcome.

Applicants' attention is directed to the decision in *In re Shokal,* 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, one of skill in the art cannot envision the detailed chemical structure of all of the nucleic acids encompassed by the claimed methods,

regardless of the complexity or simplicity of the method of isolation or use. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a representative number of polymorphic sites in the protein C sequence that are associated with the ability of the subject to recover from an inflammatory condition.

7. Claims 1-2, 4, 10-14, 16, 18-20, 22-23, 32-34, 36, 44-47, 60-61, 68, 88, and 90-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

A method of treating SIRS in a human subject, the method comprising: obtaining a nucleic acid sample from said subject; assaying said nucleic acid sample to determine the identity of the alleles present at position 4732 of SEQ ID NO: 1; determining that said patient that is homozygous for the C allele or heterozygous for the C/T alleles at position 4732 of SEQ ID NO: 1 is at risk for decreased survival and increased multiple organ dysfunction; and administering to said subject activated protein C.

does not reasonably provide enablement for claims which encompass (a) non-human subjects; (ii) any type of inflammatory condition; (iii) any polymorphic site in the protein C gene; (iv) any candidate drug known or suspected of being useful for the treatment of an inflammatory condition; (v) any allele (A, T, C, or G) at position 4732 of SEQ ID NO: 1; (vi) any genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1; and

(vii) any combination of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

**Nature of the Invention**

The claims are drawn to methods for (i) obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition; (ii) selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition; (iii) treating SIRS in a human subject in need thereof; and (iv) identifying a human subject as risk of death in whom treatment with activated protein C decreases said risk. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

**The breadth of the claims**

Claims 1, 2, 4, 10, 11-14, 16, 18-20, and 22-23 are drawn to a method for obtaining a prognosis for a subject having, or at risk of developing, an inflammatory condition. The method comprises determining a genotype of said subject which includes one or more polymorphic sites in the subject's protein C sequence. The wherein clause states that the genotype is indicative of an ability of the subject to recover from the inflammatory condition. In view of the word "subject" the claims encompass both human and non-human subjects. In view of the phrase "inflammatory condition" the claims

encompass any type of inflammatory condition i.e., cystic fibrosis, malaria, Lyme disease, asthma, etc. Only claims 22-23 are limited to certain types of inflammatory conditions. The claims broadly encompass detecting any polymorphic variant at one or more sites in the protein C gene that is associated with the ability of the subject to recover from the inflammatory condition. Only claims 2, 4, 16, and 18-20 define the polymorphic variant in the protein C gene that is associated with the ability of the subject to recover from the inflammatory condition in terms of structure.

Claims 32-34 are drawn to a method for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of an inflammatory condition. The method comprises determining a genotype at one or more polymorphic sites in the protein C sequence and sorting subjects based on their genotype. The wherein clause states that the genotype is indicative of an ability of the subject to recover from the inflammatory condition. In view of the word "subject" the claims encompass both human and non-human subjects. In view of the phrase "candidate drug" the claims encompass any type of drug. In view of the phrase "inflammatory condition" the claims encompass any type of inflammatory condition i.e., cystic fibrosis, malaria, Lyme disease, asthma, etc. The claims broadly encompass detecting any polymorphic variant at one or more sites in the protein C gene that is associated with the ability of the subject to recover from the inflammatory condition.

Claims 36, 44-47, 60, 61, 88, and 92-93 are drawn to a method of treating SIRS in a human subject in need thereof. The method comprises (a) selecting a human subject having a risk genotype for SIRS, when the subject has one or more of the

following genotypes at one or more of the following positions: (i) CC or CT at 4732 of SEQ ID NO:1; (ii) a genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1; or (iii) a combination of genotypes which are in linkage disequilibrium with position 4732 in SEQ ID NO:1; and (b) administering to said human subject selected in (a) an activated protein C.

Claims 90-91 are drawn to a method of identifying a human subject at risk of death in whom treatment with activated protein C decreases said risk. The method comprises: (a) selecting human subjects having an APACHE II score of >25 as an indication of the subjects' risk of death; and (b) selecting from the subjects selected in (a), those subjects who also have (i) a CC or CT at 4732 of SEQ ID NO: 1; (ii) a genotype in SEQ ID NO: 1 that is in linkage disequilibrium with position 4732 in SEQ ID NO: 1, or (iii) a combination of genotypes in SEQ ID NO: 1 that are in linkage disequilibrium with position 4732 in SEQ ID NO: 1, thereby identifying said subject.

Additionally it is noted that several claims broadly encompass a genotype in linkage disequilibrium with position 4732 of SEQ ID NO: 1. For example the claims encompass the following genotypes in LD with position 4732 of SEQ ID NO: 1: AA or AG at 4813, GG or GA at 6379, AA or AG at 6762, CC or C- at 7779, TT or TC at 8058, TT or TG at 8915 or TT or TC at 12228 of SEQ ID NO: 1.

Further it is noted that several claims broadly encompass a combination of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1. For example the claims encompass the following combinations of genotypes in LD with position 4732 of SEQ ID NO: 1: (1) CC or CA at 9198 and AA or AG at 5867; (2) CC or CA at 9198

and GG or GC at 4800; (3) AA or AG at 3220 and AA or AG at 5867; and

(4) AA or AG at 3220 and GG or GC of 4800.

**Guidance in the Specification and Working Examples**

Example 2 in the specification teaches an association between the C allele at position 4732 of SEQ ID NO: 1 and altered survival and organ dysfunction in critically ill adults with SIRS. Specifically the specification teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. The specification further discloses other polymorphic variations that are in linkage disequilibrium with position 4732. Of the polymorphisms that are in linkage disequilibrium with position 4732 only one, namely at position 4800 ($r^2$ value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome.

Example 4 in the specification is directed to whether or not treatment with activated protein C (XIGRIS) can reduce organ dysfunction in subjects who have sepsis and who have an at risk genotype of protein C such as the C allele at position 4732. The 28 day survival rates for patients who were protein C 4732 CC/CT were compared to patients who were protein C 4732 TT with and without treatment of XIGRIS. The results indicated that XIGRIS treatment increases survival (compared to no treatment) of patients who were protein C 4732 CT/CC (See Fig 7). Further the results indicated that XIGRIS treatment had virtually no effect on survival rate over 28 days in patients who were protein C 47322 TT.

The specification does not provide enablement for the claims as broadly written. For example the specification does not provide guidance on how to predictably associate any protein C genotype with the ability of a subject to recover from an inflammatory disease. Additionally the specification does not provide support for any inflammatory disease because the teachings in the specific are limited to patients with SIRS and sepsis. Further the claims encompass human and non-human subjects but the teachings in the specification are limited to humans. The specification only teaches that in human subjects with SIRS, the C allele at position 4732 of SEQ ID NO: 1 (in heterozygous or homozygous form) is correlated with decreased survival and increased multiple organ dysfunction. However some of the claims encompass detecting any allele (A, T, C or G) at position 4732 of SEQ ID NO: 1. Additionally some of the claims do not set forth which allele is associated with risk and whether or not the allele needs to be in homozygous or heterozygous form to be associated with the risk. Regarding the disclosed polymorphisms and combinations of polymorphisms that are in linkage disequilibrium with position 4732, only one, namely at position 4800 ($r^2$ value of 0.85) was evaluated within the same patient population as 4732 and also found to provide significant predictions of patient outcome. However there is no disclosed correlation between the SNP at position 4800 and increased survival when treated with XIGRIS (activated protein C). Although the specification teaches that XIGRIS treatment increases survival (compared to no treatment) of patients who were protein C 4732 CT/CC, the specification does not demonstrate that treatment with any other candidate

drug will also increase survival (compared to no treatment) of patients who were protein C 4732 CT/CC.

**The unpredictability of the art**

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The unpredictability is discussed below.

Given the large size of the protein C gene (over 10 kb), there are expected to be a numerous mutations in the protein C gene. However the specification does not teach a predictable means for distinguishing between variations in the protein C gene that are correlated with the ability to recover from an inflammatory condition and naturally occurring variations. The specification only teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ ID NO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS.

Further it is noted that the specification teaches several genotypes and combinations of genotypes that are in linkage disequilibrium with the polymorphism at position 4732. However it is highly unpredictable if these genotypes and combinations of genotypes will also be indicative of an ability of the subject to recover from an inflammatory condition. This unpredictability is highlighted by the teachings of Langdahl (Journal of Bone and Mineral Research 2000). Langdahl teaches that linkage disequilibrium between alleles is population dependent and there can be considerable variation between the frequencies at which alleles are inherited. For example the

reference sites that while one group reported that a repeat polymorphism in the IL-1RN gene was in linkage disequilibrium with the IL-1B (+3§54) polymorphism, Langdahl et al were unable to show linkage between these polymorphisms. Additionally Wall (Nature Reviews Genetics (2003) volume 4, pages 587-597) teaches that linkage disequilibrium (LD) refers to the fact that particular alleles at nearby sites can co-occur on the same haplotype more often than is expected by chance (page 587, 1st column, 1st paragraph). Wall teaches that patterns of LD are known to be noisy and unpredictable as pairs of sites tens of kilo bases apart might be in complete LD, whereas nearby sites from the same region can be in weak LD (page 587, 2nd column, last paragraph). Wall teaches that population history, population size, and population structure lead to differences in LD (page 588, 1st column, top). Wall teaches, "Measuring LD across a region is not straightforward" (box 1, last paragraph, page 588). Wall teaches it is difficult to compare results from different LD studies directly because of the variation in study design and methods of analyzing the data (page 591, 2nd column, 1st full paragraph). Wall teaches there are clear differences in LD between African's and non-Africans (page 593, 1st column). Thus Wall teaches that LD is not predictable. As such both Langdahl and Wall demonstrate the unpredictability in associating a genotype or a combination of genotypes in linkage disequilibrium with the polymorphism at position 4732 of SEQ ID NO: 1 with the ability of a subject to recover from an inflammatory condition.

Further, it is unpredictable as to whether the results obtained in human subjects could be extrapolated to other organisms. Knowledge that mutations in a gene occur in

one organism (i.e. humans) does not allow one to conclude that this gene, and mutations in this gene will also occur in other organisms and will be associated with altered survival and organ dysfunction in patients with SIRS. Here it is noted that the specification does not teach homologues of the protein C gene in a representative number of different organisms. Thus it is unpredictable as to whether the protein C gene, and particularly the T4732C mutation, will be present in other organisms and will be associated with altered survival and organ dysfunction in subjects with SIRS.

It is also unpredictable as to whether the results obtained with SIRS can be extrapolated to other inflammatory conditions. The genus of inflammatory conditions is quite large and each condition has its own pathology and etiology. Again it is noted that the teachings in the specification are limited to an association between the T4732C mutation and altered survival and organ dysfunction in patients with SIRS. Given the differences in the causes and effect of each type of inflammatory disease, one cannot extrapolate the results found in SIRS subjects to any type of inflammatory condition.

Additionally it is unpredictable as to whether the results obtained with activated protein C can be extrapolated to other candidate drugs known or suspected of being useful for the treatment of an inflammatory agent. The genus of drugs encompassed by the claims is quite large. The teachings in the specification are limited to an association between the C allele at position 4732 of SEQ ID NO: 1 and an improved response to therapy with activated protein C. There are no examples in the specification in which SIRS patients were treated with other type candidate drug. In the absence of evidence

to the contrary it is highly unpredictable how SIRS patients having at least one C allele at position 4732 of SEQ ID NO: 1 would respond to therapy with any other candidate drug.

**Quantity of Experimentation**

The specification teaches 2 variants in the protein C gene, namely at positions 4732 and 4800 of SEQ I DNO: 1, which are associated with altered survival and organ dysfunction in critically ill adults with SIRS. To identify additional variants of the protein C gene which are indicative of a subject ability to recover from an inflammatory condition would require extensive experimentation. Even if the extensive experimentation was performed, there is no assurance that any other additional variants would be found. If additional variants were found that were associated with altered survival and organ dysfunction then even more experimentation would be required to determine if individuals having those variants showed an improved response to therapy with activated protein C or any other candidate drug encompassed by the claims. Such random, trial by error experimentation is considered to be undue and highly unpredictable. The specification has provided only an invitation to experiment.

Additionally further experimentation would be required for each of the claims that encompass genotypes or combinations of genotypes in linkage disequilibrium with position 4732 of SEQ ID NO: 1. One of skill in the art would have to conduct extensive experimentation to determine if each genotype or combination of genotypes is associated with the ability to recover from an inflammatory condition. Each genotype or

combination of genotypes would have to be tested and analyzed to determine if it was statistically associated with a representative number of different types of inflammatory conditions. Even if the extensive experimentation was performed, there is no assurance that any other genotype or combination of genotypes would be found having the property of being associated with the ability to recover from the inflammatory condition. Such random, trial by error experimentation is considered to be undue and highly unpredictable. The specification has provided only an invitation to experiment.

**Conclusion**

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention in the full scope of the claims.

8. It is noted that the claims rejected below have been rejected under 35 USC 102 as anticipated by the prior art and they have been rejected under 35 USC 112 1st paragraph as not fully described or enabled by the specification as originally filed. In the instant case, where the prior art does anticipate particular embodiments of the broadly claimed methods, the prior art is not sufficient to provide an adequate written

description of the breadth of the claims, nor is the prior art sufficient to enable the skilled artisan to practice the claimed method in the full scope of the claims.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Spek (The Journal of Biological Chemistry 1995 Vol 270 No 41 pages 24216-24221). This reference is already of record.

Regarding Claim 1 Spek teaches a method comprising determining a genotype of a subject that includes one or more polymorphic sites in the subjects protein C sequence (abstract, page 24217). While Spek teaches all of the claimed method steps, Spek does not provide enablement for a method of obtaining a prognosis for a subject having, or at risk of developing, an inflammatory disease. Particularly Spek does not teach a correlation between the genotype and the ability of the subject to recover from an inflammatory condition. However this art rejection is set forth because it teaches a broad interpretation of the claims which does not require such a correlation. In the instant case the preamble is considered to be an intended use of the claimed method

and the limitation that the genotype is indicative of an ability of the subject to recover from an inflammatory condition is broadly interpreted as a property of the genotype. This rejection could be overcome by amending the claim to recite an active process step of requiring the correlation e.g., determining that said human individual has an increased ability to recover from the inflammatory disease when the genotype is detected.

Regarding Claim 10 Spek teaches obtaining protein C sequence information for the subject.

Regarding Claim 11 Spek teaches that the genotype is determined using a nucleic acid sample from the subject.

Regarding Claim 12 Spek teaches obtaining the nucleic acid sample from the subject.

Regarding Claim 13 Spek teaches a method wherein the genotype is determined using RFLP.

***Response To Arguments***

11. In the response filed April 8, 2011, Applicants traversed the enablement rejection.

The Applicants state that the claims have been amended to refer only to human subjects.

This argument has been fully considered. Several of the previously withdrawn claims which are now being examined broadly recite the word "subjects" which encompasses both human and non-human subjects.

The Applicants argue that they disagree with the Office's position regarding the non-enablement of sepsis and septic shock.

These arguments have been fully considered and is considered persuasive. However it is noted that several of the previously withdrawn claims which are now being examined broadly recite the phrase "inflammatory condition" which encompasses a large genus of conditions. While the specification provides support for SIRS and sepsis, there is no such support for asthma, Chron's disease, HIV, eclampsia etc

The Applicants argue that as amended the claims recite the risk alleles at each position.

This argument has been fully considered. Several of the previously withdrawn claims which are now being examined encompass detecting any allele in homozygous or heterozygous form at each position.

Additionally the claims are rejected for encompassing the detection of genotypes in linkage disequilibrium with position 4732 for the reasons stated in the rejection above.

***Conclusion***

12. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Amanda M. Shaw/
Primary Examiner
Art Unit 1634